BAG report_Nury (08/09/21-10/09/21)

The session was used to collect a dataset on a pentameric membrane protein formed of two subunits: the serotonin 5-HT3AB receptor. Over the years, we have solved a number of structures of the homomeric receptor that comprises only one type of subunit, first using CM01 then at the IBS Glacios after the K2 installation. This allowed to explore its structural pharmacology. To go further, we need this step of going from homomers to heteromers, as native human serotonin 5-HT3 receptors are mostly heteromers. The main difficulties are two-fold: expressing it (and I think we solved that difficulty in 2021) and recognizing the quite similar subunits during data treatment. We hoped that, using the large number of images accumulated during a CM01 session, we could apply tricks to discriminate the A and the B subunits. Alas, even though we had inserted a marker at the gene level (a fusion protein on the B subunit) it was not the case, probably because the fused domain was too flexible relative to the receptor. So even if we can derived 3 Å reconstructions from the dataset (in C5 and also in C1), we have not been able to obtain one that we could reliably assign to an heteromeric receptor. We are now investigating constructs with a tighter link between the subunit and the marker.
Work done by Uriel Lopez-Sanchez at the IBS with the help of the facility.

Zarkadas E., Pebay-Peyroula E., Thompson M.J., Schoehn G., Uchański T., Steyaert J., Chipot C., Dehez F., Baenziger J.E, Nury H (2022) Conformational transitions and ligand-binding to a muscle-type nicotinic acetylcholine receptor *Neuron 2022, in the press*